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Sphincter-saving surgery for failed organ preservation after a neoadjuvant therapy and radiation boost: A surgeon's perspective

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Abstract

Purpose This study investigates the functional outcomes of patients with low rectal cancer undergoing inter-sphincteric resection (ISR) following brachytherapy boost radiotherapy (BoRT), compared to those who underwent ISR after standard chemoradiotherapy. BoRT is an alternative to total neoadjuvant therapy for increasing organ preservation rates in low rectal cancers. However, its impact on sphincter function following stoma reversal remains unclear.

Method The study involved a retrospective analysis of 145 patients treated at a single institution between 2013 and 2021. Eighteen patients received pre-operative BoRT and were compared with 127 patients who did not, using propensity score matching based on age, sex, body mass index, and tumor distance from the anal verge with match ratio 1:4. Functional outcomes were assessed six months post-stoma reversal using the Low Anterior Resection Syndrome (LARS) Score, Wexner Score, and Kirwan Grade.

Results The results revealed that patients in the boost RT group had significantly worse functional outcomes, with a median LARS score of 36 (very high) compared to 10 in the no boost group ($p < 0.001$). Similarly, the median Wexner score was higher in the boost RT group (17 vs. 8, $p < 0.001$). The Kirwan Grade was consistent across both groups.

Conclusion This study highlights the detrimental impact of BoRT on functional status, underscoring the importance of comprehensive patient counselling before initiating BoRT in candidates eligible for sphincter preservation. If optimal outcomes are not achieved following brachytherapy boost, surgical options like ISR or APR should be thoroughly discussed with patients to ensure informed decision-making.

Keywords Brachytherapy boost radiotherapy, Contact X ray brachytherapy, Intersphincteric resection, Salvage surgery, Sphincter preservation

Introduction

In recent years, non-surgical management of low rectal cancer has increased, thanks to concept of Total neoadjuvant therapy (TNT) [1] and intensified dose of radiotherapy [2]. This includes either induction or consolidation chemotherapy to either long course [3] or short course radiotherapy [4]. Brachytherapy Boost radiotherapy (BoRT) or contact brachytherapy (CXB) has been employed in selective centres to improve organ

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preservation [2, 5]. Intensifying treatment may have an impact on sphincter function. So, while the focus is on patients who have organ preservation including functional outcomes, the group of patients who fail organ preservation and need surgery are often ignored by enthusiast of wait and watch. As a surgeon who offers Intersphincteric resection (ISR) for failed organ preservation, often in young patients, functional outcomes after stoma reversal are crucial. Hence the decision to intensify treatment for low rectal cancers (eligible for ISR / sphincter preservation) for organ preservation is based on choosing between options of consolidation chemotherapy or BoRT.

In case of ISR, resting anal pressure falls and is dependent on external anal sphincter [6]. Giving BoRT may damage external anal sphincter causing lowering of resting and squeeze pressure leading to incontinence [7, 8]. This is less likely to happen after consolidation chemotherapy alone [1]. The present study aims to assess the functional outcomes observed in the patients who undergo salvage therapy after BoRT. We intend to underscore the delicate balance that is needed between oncological outcomes and quality of life outcomes in patients with rectal cancer i.e. choosing between consolidation chemotherapy and BoRT in tumors eligible for sphincter preservation, if they go on wait and watch route.

Materials and methods

Study design, settings and patients

Retrospective analysis of prospectively maintained ISR database from a high-volume colorectal cancer unit between March, 2013 and July, 2023. ISR of histologies other than rectal adenocarcinoma was excluded (i.e. melanoma, neuroendocrine tumors, gastrointestinal stromal tumors). Patients who had non-reversed stoma, lost to follow up, expired or who did not give consent to answer the questionnaire for functional score assessment were excluded from the study. Patients were subjected to the functional assessment only if they are at least 6 months post-surgery and those within 6 months period were excluded from the study.

Treatment

Patients with low rectal cancers as primary with or without metastasis were subjected to the neoadjuvant treatment with one of the two radiation protocols — long course chemoradiation (50Gy in 25 fractions with concurrent capecitabine) or short-course radiation (25Gy in 5 fractions) with 4 cycles of consolidation chemotherapy after discussion in the multi-disciplinary tumor board meeting. All patients underwent chemotherapy-based radiotherapy planning using rotational arc-based intensity-modulated radiotherapy (IMRT) with Target volume contouring based on Valentini et al. consensus guidelines. [9] Segmentation of Organs at Risk (OAR) was done according to UK-BFCO Consensus guidelines. The gross tumor volume (GTV): primary or gross nodes was boosted to doses of 30 Gray in 5 fractions while the dose to clinical target volume (CTV) pelvis was up to 25 Gy in 5 fractions. The plan evaluation for the coverage and OAR constraints were done as per international anorectal radiotherapy standard guidelines and were accepted with up to 10% individual patient variation [10]. The deviation from predetermined dose constraints was reported as acceptable (10%), minor (10–20%) and major deviations(> 20%). The option of two regimens was based on logistics, availability of radiation slots, and patients' inability to stay locally for LCRT.

At the end radiotherapy or SCRT and 2 cycles of chemotherapy, the radiation oncologist performed a digital rectal examination (DRE) and rigid proctoscopy to assess the response and feasibility of BoRT (only likely good responders) by noting the total volume reduction. Re-assessment was done six to eight weeks after end of neoadjuvant therapy by pelvic magnetic resonance imaging (MRI), digital rectal examination and flexible sigmoidoscopy in selected cases (if clinically or near complete response). Nodal status was determined with the help radiologists specializing in gastrointestinal radiology. Criteria for EMLN positivity comprised: (i) size criteria alone if the short axis dimensions (SAD) was ≥ 7 mm or (ii) SAD of ≥ 5 mm along with two or more additional morphological features, such as rounded shape, irregular border or heterogeneous signal intensity. The decision to finally treat suspicious EMLN was taken after deliberation in multidisciplinary team meetings with the radiation oncologist, surgeon and radiologist in attendance. Response evaluation was performed on MRI done 6–8 weeks from completion of NACTRT. Nodal shrinkage was the only objective criterion used to quantify response, where a SAD < 5 mm was considered a good response.

External beam radiotherapy (EBRT) was planned on contrast-enhanced computed tomography scans. These were registered with planning MRI scans on the treatment planning system to aid with the contouring of GTV at the primary as well as EMLN (GTVn). The CTV consisted of the mesorectum, the lateral group of lymph nodes and the presacral space up to the bifurcation of common iliac arteries. The common iliac, external iliac and inguinal nodal regions were included in accordance with established consensus guidelines for target volume delineation. Planning target volumes (PTV) were generated with isotropic margins of 5 mm around the CTV (PTVp) and 5–7 mm around GTVn (PTVn). Doses ranging from 45 to 50 Gy were prescribed to PTVp, with

Table 1 Baseline characteristics, after propensity matching

Characteristic		Boost RT[a]	No Boost	*P* value
Age	Median (IQR[b])	48.5 (37.8 to 61.8)	49.5 (38.0 to 55.2)	0.538
Sex	Male	12 (66.7)	48 (66.7)	1.000
	Female	6 (33.3)	24 (33.3)	
ASA[c]	1	11 (61.1)	44 (61.1)	0.879
	2	7 (38.9)	27 (37.5)	
	3	0 (0.0)	1 (1.4)	
BMI[d]	Median (IQR[b])	23.1 (22.1 to 24.3)	23.7 (21.9 to 25.5)	0.643
Distance of tumor from AV[X]	Median (IQR[b])	3.5 (3.0 to 4.8)	3.5 (2.0 to 4.2)	0.943
Pre-Operative TNM[e] **Stage**				
T	T2	2 (11.1)	19 (26.4)	0.353
	T3	15 (83.3)	51 (70.8)	
	T4	1 (5.6)	2 (2.8)	
N	N0	2 (11.1)	22 (30.6)	0.247
	N1	10 (55.6)	32 (44.4)	
	N2	6 (33.3)	18 (25.0)	
M	M0	18 (100.0)	69 (95.8)	0.883
	M1	0 (0.0)	3 (4.2)	
MRF[f]	Positive	7 (38.9)	8 (11.1)	0.010
	Negative	11 (61.1)	64 (88.9)	
PDSR[g] **Positive**	Yes	1 (5.6)	9 (12.5)	0.675
	No	17 (94.4)	63 (87.5)	
RT[a]	LCRT[h]	14 (77.8)	51 (70.8)	0.769
	SCRT[i]	4 (22.2)	21 (29.2)	

Radiotherapy[a], Interquartile range[b], American society of anaesthesiology[c], Body mass index[d], Anal verge, Tumor Node Metastasis[e], Mesorectal fascia[f], Poorly differentiated with signet ring morphology[g], Long course radiotherapy[h], Short course radiotherapy[i]

PTVn receiving between 57 and 60 Gy in 25 fractions, 5 days/week over 5 weeks, depending on the proximity of the SIB volume to organs at risk. Concomitant chemotherapy consisted of oral capecitabine (825 mg/ m2 orally twice daily, 5 days/week) monotherapy initiated on day 1. In summary, BoRT was given in the form of brachytherapy and in few cases as simultaneous integrated boost (SIB) [11]. Weekly MRI guided brachytherapy planning followed by intraluminal brachytherapy using an indigenously developed endoluminal applicator to doses of 7–10 Gy/fraction aiming at a target cumulative BED of 95 Gy (a/b 10) as the maximum dose.

The first response assessment comprising of DRE, sigmoidoscopy and pelvic MRI was done at 8–12 weeks after TNT completion for further decision of non-operative management. A complete clinical response or near complete clinical response with no regrowth were selected for wait and watch. Patients who did not undergo wait and watch or clinical complete response/ and were eligible for sphincter preservation underwent ISR. Surgery was planned within 6–10 weeks after completion of preoperative treatment. Total mesorectal excision (TME) with ISR was performed according to a standardized technique by laparoscopic, robotic or open approach [12]. The resected specimens were analysed by pathologist where incomplete microscopical resection (R1) was defined as a CRM of ≤ 1 mm from the inked non-peritonealised surface of the specimen [13]. The standardized five-point Mandard tumor regression grading (TRG) was used to assess the tumor response [14]. Stoma closure was performed at end of adjuvant therapy or 3 months post-surgery.

Variables

After propensity matching, the demographic characteristics and malignancy related variables recorded were age, sex, ASA (American Society of Anaesthesiology) score, BMI (body mass index), distance of tumor from anal verge, clinical TNM (tumor, node and metastasis) stage. Treatment related variable recorded was type of neo-adjuvant radiotherapy (long or short course, LCRT or SCRT) (Table 1). Post-operative histopathology related variables were involvement of meso-rectal fascia, circumferential resection and distal margin, worse histology (poorly differentiated adenocarcinoma, PDAC) (Table 2). Variables for functional assessment

Table 2 Results after propensity score matching with match ratio of 1:4

Characteristic		Boost RT[a]	No Boost	*P* value
CRM[b]	NEGATIVE	17 (94.4)	72 (100.0)	0.451
	POSITIVE	1 (5.6)	0 (0.0)	
Distal Margin	Median (IQR[c])	2.0 (1.0 to 2.0)	1.0 (1.0 to 2.0)	0.532
LARS[d] **score**	Median (IQR[c])	36.0 (28.2 to 37.5)	10.0 (6.0 to 26.0)	< 0.001
Wexner score	Median (IQR[c])	17.0 (14.0 to 20.0)	8.0 (6.0 to 10.0)	< 0.001
Kirwan Grade	I	1 (5.6)	6 (8.3)	0.121
	II	2 (11.1)	27 (37.5)	
	III	13 (72.2)	36 (50.0)	
	IV	2 (11.1)	3 (4.2)	

Radiotherapy[a], Circumferential resection margin[b], Interquartile range[c], Low anterior resection syndrome[d]

LARS (Low anterior resection syndrome) and Wexner scores and Kirwan grade [10–12] (Table 2).

Outcomes

After a minimum of six months post-stoma closure, patients were evaluated in the out-patient department and their consent for functional evaluation was sought as a part of routine audit. Functional assessment scores were evaluated according to the standard questionnaires i.e. Low anterior resection syndrome (LARS) score [15] (a systematic questionnaire to assess the need for frequent motions and incontinence), Wexner score [16] (a score of 0–20, with 0–4 points based on severity of incontinence to solid, liquid, gas, need to wear pad and lifestyle alteration) and Kirwan grade [17] (Grades A to D based on severity of incontinence).

Statistical methods

All the data were entered and analyzed in the statistical program for social sciences (SPSS, IBM, version 26). Regarding the continuous variables, interquartile range (IQR) and medians were calculated. Propensity score matching was done between the two cohorts with and without BoRT. Matching was executed using the age, sex, BMI and distance of tumor from anal verge. Matching ratio used was 1:4.

Ethics

This study was a retrospective study, and functional assessment is a part of routine clinical care. The study protocol was according to the standards of 1964 Helsinki Declaration and its latest amendment (2013). Ethical approval has been obtained for a larger study of outcome assessment for ISR by our Ethics committee and the current study is a subset analysis of the larger approved study. Study reporting was done according to the STROBE (Strengthening the reporting of observational studies) guidelines.

Results

Over a period of 10 year and 4 months, 397 ISR procedures were performed. Of these, 145 patients met the inclusion criteria for functional assessment. BoRT was administered to 18 patients, and 127 did not receive any boost. After propensity matching, 90 patients were included in the final analysis—18 who received BoRT and 72 who did not. The median ages in both the BoRT and no-BoRT groups were similar (48.5 vs. 49.5 years). Gender distribution was equal in both groups ($p=1.00$). Median BMI (23.1 kg/m2 vs. 23.7 kg/m2; $p=0.643$) and the distance of the tumor from the anal verge (3.5 cm in both groups; $p=0.943$) were also similar.

The no-BoRT group had a higher number of patients with clinical T2 stage (11% vs. 26.4%) and Poorly differentiated adenocarcinoma,signet ring morphology (12.5% vs. 5.6%; $p=0.675$), while the BoRT group had more advanced tumor, clinical T3 and T4 stage cancers (83.3% vs. 70.8% and 5.6% vs. 2.8%, respectively), nodal positivity (55.6% vs. 44.4%; $p=0.247$) and MRF positivity (38.9% vs. 11.1%; $p=0.01$). An equivalent number of patients in both groups received LCRT and SCRT as part of neoadjuvant treatment. None of the patients in the no-BoRT group had CRM positivity (5.6% vs. 0%).

During the study period, the functional challenges faced by the patients were systematically recorded as scores, namely LARS, Wexner score and kirwan score which were significantly higher in the BoRT group. Median LARS scores were 36 vs. 10 ($p<0.001$), and Wexner scores were 17 vs. 8 ($p<0.001$) for the BoRT vs. no BoRT groups, respectively. These findings are illustrated in the box plot graphs (Figs. 1 and 2).

Discussion

Using organ preserving strategies for low rectal cancer have assumed importance avoiding need for surgery and its associated adverse outcomes like leaks, urinary and sexual function and LARS. The various options of organ preservation include TNT by addition of chemotherapy (OPRA) or radiotherapy dose intensification using CXB (OPERA) [1, 2]. While functional outcomes after successful organ preservation in both arms is very good, functional outcomes of patients undergoing sphincter preserving salvage therapy is unknown. As a surgeon, choosing the right modality for patients who are eligible for sphincter preservation is important. Our study shows

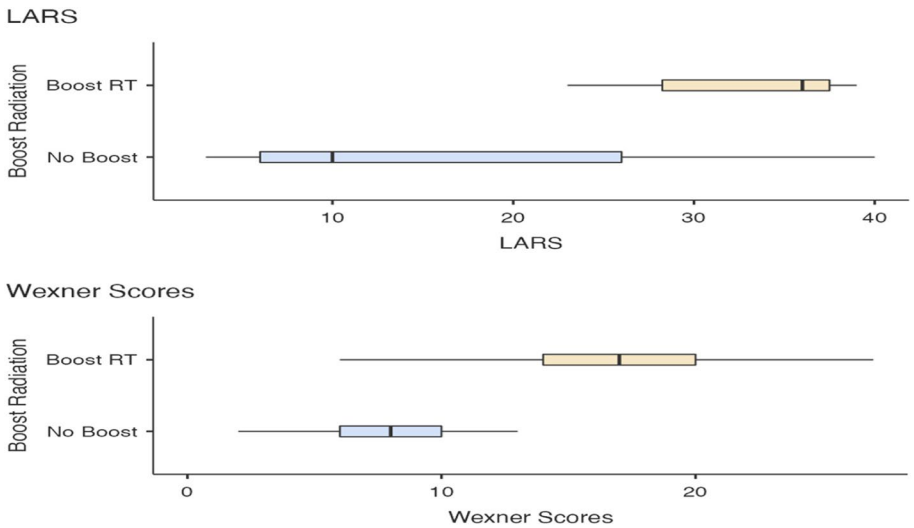

Fig. 1 Box plot comparing functional outcomes between the boost radiotherapy and no boost groups, based on Low Anterior Resection Syndrome (LARS) and Wexner scores

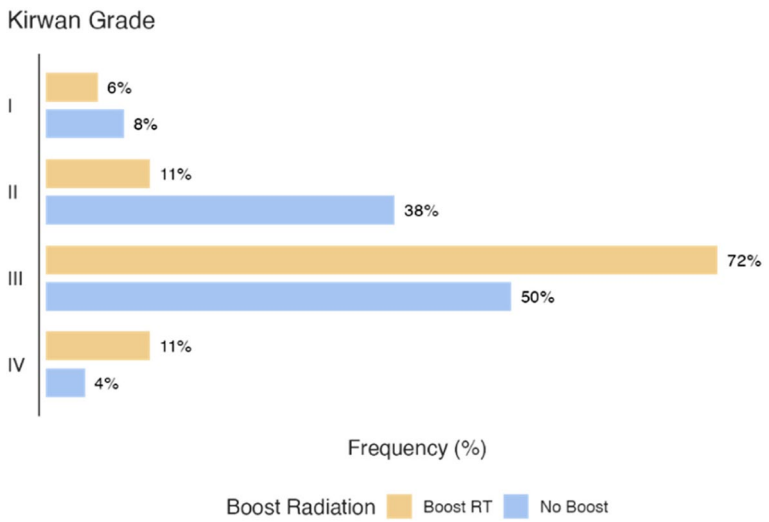

Fig. 2 Comparison of Kirwan grades between the boost radiotherapy group and the no boost group

functional outcomes of salvage ISR after failed organ preservation with BoRT is suboptimal with Median LARS scores of 36 vs. 10 ($p<0.001$), and Wexner scores of 17 vs. 8 ($p<0.001$) for the BoRT vs. no-BoRT groups, respectively.

The functional outcomes of BoRT group in our study were inferior due to intensification of radiotherapy in a group of patients with advanced tumors (BoRT Group). After going through the published literature, it was found that the effect of BoRT on sphincter function (post salvage ISR) has never been addressed. Advancements in surgical techniques and radiation therapy (RT), along with the utilization of various radiation methods, often make it challenging to accurately interpret information regarding adverse effects [18] and the addition of chemotherapy makes these relations to radiotherapy even more complex [19]. It is concerning that certain serious adverse effects, such as bowel obstruction and the development of second cancers, may manifest more than five years after the initiation of treatment. This underscores the critical need for the careful design and implementation of long-term follow-up protocols in all randomized trials involving radiation therapy for rectal cancer [18]. Ensuring long term survivors of ISR maintain good quality of

life and sphincter function is paramount. This has to be compared to consolidation chemotherapy in TNT with its associated long-term toxicity of neuropathy and functional impairment and its impact on occupation (skilled personal like musicians, artist or even typing) [2]. The level of functional impairment is different for different occupations.

The primary objective of RT is to mitigate the risk of local recurrence. Typically, the target volume for RT encompasses the primary tumor, along with the mesorectal and pre-sacral lymph nodes. Additionally, lymph nodes along the obturator, medial rectal, and internal iliac arteries are included, and if the tumor is situated in the lower rectum, nodes along the pudendal and inferior rectal arteries are also incorporated [20]. The anal canal is irradiated exclusively in cases of low rectal cancers necessitating an APR [21].

In the OPERA trial [2], organ preservation rate was very high (> 90%) for small size (< 3 cm) tumor, which was achieved without increased toxicity and with good rectal function. Patients with partial response underwent radical TME (total meso-rectal excision) (2). The bowel function assessment with the LARS score was done only for the patients without radical proctectomy unlike the present study where we have assessed the functional score in the post-surgery status.

Throughout the study period, majority of the patients in the BoRT group faced significant difficulties in maintaining a pad-free status, even during routine household activities. They expressed feelings of social dissatisfaction and embarrassment when going out for work due to involuntary episodes of flatus and faecal discharge. They had higher functional scores comparted to no-BoRT group. Our philosophy for patient selection for BoRT in patients with complete or near complete response is to consider the distance of tumor from the anal verge, personal and professional lifestyle of the patient and its related perceived impairment. A planned low anterior resection or an ultra-low anterior resection works in congruence with the impartment of BoRT. A thorough counselling helps the patients in informed decision. If ISR is inevitable, a wiser option of chemotherapy as a modality of TNT may be employed in an attempt to avoid the sphincter dysfunction secondary to BoRT.

Our study has several merits. It addresses a significant gap in the existing literature. Most research on BoRT focuses on the functional outcomes of patients who achieve cCR and are kept on the WW approach, often gauging the safety of BoRT based on this subset. To our knowledge, no publication specifically examines the functional outcomes of patients who, after BoRT, do not achieve cCR and subsequently undergo surgery. We conducted long-term follow-up on patients operated on during the initial tenure of the study, adopting a patient-centric approach to improve the long-term functional outcomes of rectal cancer survivors. Our study uses multiple validated scoring systems to provide a robust and multidimensional assessment of functional outcomes, enhancing the reliability and depth of our findings.

However, our study is not without drawbacks. The number of patients in the BoRT group is relatively small ($n = 18$), making it difficult to draw clear conclusions based on this sample size. The patient selection for BoRT was highly individualized, hence a fair comparative analysis is not possible. This precludes direct comparisons between groups and necessitates propensity score matching. A larger sample size would be crucial for a more precise evaluation of BoRT's impact on post-ISR functional outcomes. Additionally, since patients were selected for the boost based on response assessment, those with and without boost likely had different patient and tumor characteristics, potentially leading to differences in functional outcomes. Propensity matching with such a small sample size does not fully account for these confounding factors. Thus, this study is more of observational rather than comparative, and hypothesis-generating rather than conclusive. The absence of anal manometry in this study limits a comprehensive understanding. The functional assessment criteria were stringent; however, recorded at a single point. A more dynamic evaluation at intervals such as 3 months, 6 months, 1 year, or 3 years could provide a clearer trajectory of functional improvements for each patient. Survivor bias could not be eliminated as only patients eligible for functional assessment (alive, free from local recurrence, Not lost to follow-up, agreed for functional assessment) could be assessed.

While this study casts a negative light on increased radiation doses for salvage sphincter-saving surgery after a failed watch-and-wait approach, the alternative of consolidation therapy and sphincter-saving salvage surgery also shows suboptimal local recurrence-free survival. Therefore, after a failed watch-and-wait approach, abdominoperineal resection might be the most viable option for balancing disease control and recurrence [22]. Patients considering the watch-and-wait approach should exercise informed judgment when choosing between various options.

Conclusions

This study highlights the detrimental impact of BoRT on functional status underscoring the importance of comprehensive patient counselling before initiating BoRT in candidates eligible for sphincter preservation. If optimal outcomes are not achieved following brachytherapy boost, surgical options like sphincter saving surgery or

APR should be thoroughly discussed with patients to ensure informed decision making.

Abbreviations

APR	Abdominoperineal resection
ASA	American society of anaesthesiology
BMI	Body mass index
BoRT	Brachytherapy Boost radiotherapy
cCR	Clinical complete response
CRM	Circumferential resection margin
ISR	Intersphincteric resection
IQR	Inter quartile range
LARS	Low anterior resection syndrome
LCRT	Long course chemoradiotherapy
MRF	Mesorectal fascia
OP	Organ preservation
RT	Radiotherapy
SCRT	Short course radiotherapy
SPSS	Statistical program for social sciences
STROBE	Strengthening the reporting of observational studies
TNT	Total neo-adjuvant therapy
TNM	Tumor, node and metastasis
WW	Watch and wait

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Patient consent
No specific consent statement was obtained as the functional assessment was done as a part of the survivorship program. Additionally, consent was waived in accordance with the Medical Council of India's Code of Medical Ethics (17.17), which permits such waivers for retrospective studies with minimal risks when patient identities are not disclosed. Additionally, it was waived by the ethics committee.

Authors' contributions
This study is conceptualized, designed critically revised by Avanish Saklani. Abdeali Saif Arif Kaderi and Sanjay Singh contributed equally to writing of this manuscript and are co-first authors. Mufaddal Kazi has done the analysis and interpretation of data. Ankit Sharma, Ashwin Desouza, Suman Kumar Ankathi, and Avanish Saklani have read and approved the final version of this manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethics Committee approval was taken for outcome assessment of Intersphincteric resection under the title- "A study to assess the functional outcome and quality of life after sphincter preserving surgery in low rectal cancer patients at Tata Memorial Hospital, Mumbai.", Project numbered " 3030 (IEC2) " with project form numbered "AX1-V6.1/SOP03/V6.1 "with a validity upto 10/11/2026. The current study is a subset of the larger study approved by the TMC IEC (Tata Memorial Center-Institutional Ethics Committee).

Competing interests
The authors declare no competing interests.

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